77. (Once Amended) The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 is ICAM-1 of a myelomonocytic cell line having a molecular weight of [about] 114 kDa as determined by SDS polyacrylamide gel electrophoresis.

D2 Cont

78. (Once Amended) The purified or isolated ICAM-1 preparation as claimed in claim 71, wherein said purified or isolated ICAM-1 is fibroblast ICAM-1 having a molecular weight of [about] 97 kDa as determined by SDS polyacrylamide gel electrophoresis.

Sub E2

80. (Once Amended) A lipid membrane comprising isolated or purified ICAM-1 substantially free of natural protein contaminants, wherein said isolated or purified ICAM-1 is [in a biologically active form] capable of binding to LFA-1, Mac-1, or p150,95.

D3

81. (Twice Amended) The lipid membrane as claimed in claim 80, wherein said ICAM-1 specifically binds to [at least one ligand selected from the group consisting of:] LFA-1.

Remarks

Reexamination and reconsideration of this application are respectfully requested. In this amendment claim 74 has been canceled. Moreover, claims 87-98 have been withdrawn from consideration pursuant to a restriction requirement. Thus, after then entry of this amendment, claims 71-73 and 75-83 will be pending and subject to examination in this application.

Applicants have amended claims 75-78 to recite that the given molecular weights of ICAM-1 are as determined by SDS polyacrylamide gel electrophoresis. Exemplary support for

this amendment can be found in the specification at page 66, lines 13-14. Claims 71 and 80 have been amended to recite that the purified or isolated ICAM-1 is capable of binding to LFA-1, Mac-1, or p150,95. Exemplary support for this amendment can be found in the specification at page 2, lines 12-26, and at page 16, lines 8-14.[1] Consequently, no new matter has been added.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Restriction Requirement

At pages 2-3, items 1-2, of Paper No. 9, the Examiner states that "[U]pon reconsideration, the prior restriction requirement is reimposed for the reasons previously set forth. Additionally, due to the different laboratories involved in investigation of properties of ICAM-1-like molecules, too much search burden would be imposed in examination of distinct methods of use or preparation of ICAM-1 molecules." Therefore, the restriction requirement has now been reimposed and made final. Consistent with this final restriction requirement, Applicants are hereby pursuing constructively elected claims 71-83. While Applicants submit that it would not constitute an undue burden to examine all claims together, claims 87-98 have been withdrawn from consideration as corresponding to the non-elected invention. Applicants reserve their right to prosecute claims directed to a non-elected invention in this or a continuing application.

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[1] Support for this amendment can also be found in the priority application 07/045,963 filed May 4, 1987 at page 11, line 17-page 12, line 2, and at page 13, lines 9-14 of the specification.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

At pages 3-6, items 3A-3H, of Paper No. 9, the Examiner maintains in part the rejection of claims 71-83 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants hereby acknowledge the Examiner's withdrawal of the previous rejections under items 2A-E, and 2 G-H at pages 3-6 of Paper No. 9.[2]

At page 5, item 3F, of Paper No. 9, the Examiner has objected to the use of the term "about" in claims 75-78 as it is allegedly vague and indefinite. Applicants respectfully traverse this ground for rejection.

Specifically, the Examiner contends that:

> (1) Is this term limited to 1%, 5%, 10%, 100% or less variation in the recited molecular masses?... (2) Is this intended to encompass a family of native ICAM-1 molecules with slightly different molecular masses as purified, e.g. by virtue of different degrees of glycosylation or expression of alternatively processed mRNA transcripts? (Office Action at page 5, item F).

Applicants note that the Examiner has not presented any evidence or reasons to rebut Applicants' arguments presented in the response filed October 15, 1997. Rather, the Examiner has simply restated that "[A]pplicants' comments on pages 8-9 of the response have been considered, but do not adequately indicate the scope of this term." According to the Manual of

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[2] Applicants note that in item 3D, the Examiner has withdrawn the rejection of claims 71, 80, 81, and 84-86 under 35 U.S.C. § 112, second paragraph. Applicants submit that, in view of the cancellation of claims 84-86 in the response filed October 15, 1997, withdrawal of the rejection regarding the scope of the term "biological activity" or "biologically active" no longer applies to claims 84-86.

Patent Examining Procedure (M.P.E.P.) § 706.07(a), a final rejection should include a "rebuttal of any arguments raised in Applicants' response."

Nevertheless, without acquiescing in the propriety of the rejection, however, and solely to advance prosecution, claims 75-78 have been amended to recite that the molecular weight of ICAM-1 varies within specified ranges as determined by SDS polyacrylamide gel electrophoresis, depending upon the cell source from which ICAM-1 is immunoprecipitated. Applicants submit that, as stated in the specification at page 66, lines 13-18:

> ICAM-1 purified from human spleen migrates in SDS-polyacrylamide gels as a broad band of M_r of 72,000 to 91,000. ICAM-1 purified from JY cells also migrates as a broad band of M_r of 76,500 to 97,000. These M_r are within the reported range for ICAM-1 immunoprecipitated from different cell sources: M_r=90,000 for JY cells, 114,000 on the myelomonocytic cell line U937, and 97,000 on fibroblasts (Dustin et al., J. Immunol. 137:245 (1986)).[3]

Accordingly, in view of the amendment to claims 75-78, Applicants submit that this rejection is now moot, and withdrawal thereof is respectfully requested.

III. Rejections Under 35 U.S.C. § 112, First Paragraph

At pages 6-9, items 4A-D of Paper No. 9, the Examiner rejects claims 71-83 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner's rationale

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[3] Support is also found in the priority U.S. Patent Application Serial No. 07/045,963 in the specification at page 58, lines 7-16.

for this rejection is set forth on pages 6-9 of Paper No. 9. The Examiner provides four reasons to support this rejection.

First, the Examiner contends that:

> The specification only describes ICAM-1 having the sequence set forth by Fig. 8. No other amino acid sequences for native ICAM-1 products with different sequences are described. Applicant indicates on page 10 of the response that ICAM with different molecular masses can be obtained using the methods described in the specification, e.g. by immunoprecipitation from different sources. However, the specification does not describe the critical structural characteristics of such other species of ICAM-1 and therefore represents an invitation to obtain other structurally-distinct forms of ICAM-1 of Fig. 8. Whether such other forms of ICAM-1 would have identical functional properties to the ICAM-1 of Fig. 8 or retain critical structural properties, e.g. ability to bind HRV or LFA-1 would be unpredictable. Further, it is unclear how much structure would have to be retained between an ICAM-1 variant and the ICAM-1 of Fig. 8 in order for it to be considered ICAM-1. (Office Action at page 7, of paper No. 9).

Applicants respectfully traverse this ground for rejection.

Second, the Examiner contends that "[t]he specification does not adequately describe which preparations of ICAM-1 retain particular biological properties such as the ability to bind LFA-1, lymphocytes or HRV. Applicants' argument on page 11 is persuasive with respect to the ICAM-1 of Fig. 8, but not with respect to other ICAM-1 variants which have not been structurally and functionally described." (Paper No. 9, item 4B at Page 8). Applicants respectfully traverse this ground for rejection.

Third, the Examiner also alleges that the specification "only describes particular molecules on the surface of lymphocytes, such as LFA-1 or members of the LFA-1 family, which bind to ICAM-1. Applicants' comments have been considered, but in view of the broad intended definition of "biological activity" set forth in the Applicants' response to the rejection under 112/2

this rejection is maintained." (Paper No. 9, item 4C at page 8). Applicants respectfully traverse this ground for rejection.

Finally, the Examiner contends that "[t]he rejection set forth in section 6D of the last action is maintained in view of the broad scope of the term "biological activity". In the previous Office Action, the Examiner had rejected claims 80-83 under 35 U.S.C. § 112, first paragraph, for allegedly being enabled only for those forms of ICAM-1 products, lipid membranes, and methods of incorporation disclosed on page 85-87 of the specification.

The rationale for the Examiner's rejection was set forth on page 7, item 6D of Paper No. 6. In short, the Examiner alleged that "use of different domains of ICAM-1 would impart different binding characteristics. Use of different types of lipids would result in different stabilities and configurations of ICAM-1 within a membrane and result in a product with unpredictable stability, bioavailability and binding properties." (Paper No. 6, item 6D at page 7). The Examiner now concludes, however, that "[t]his rejection would be withdrawn if the claim language were limited to products with a demonstrated structure function relationship with a recited biological activity, such as the ability of residues in domains 1 and 2 to bind to LFA-1 or HRV." (Paper No 9, item 4D at 9). Applicants respectfully traverse this ground for rejection.

Nevertheless, without acquiescing in the propriety of the rejection, and solely to advance prosecution, Applicants have amended claims 71 and 80 to recite that the purified or isolated ICAM-1 preparation can specifically bind to members of the LFA-1 family. Accordingly, in view of the amendments to claims 71 and 80, Applicants submit that this ground for rejection has been rendered moot. Withdrawal of this rejection is therefore respectfully requested.

IV. Rejection under 35 U.S.C. § 102(a) or (b)

At Pages 9-10, item 5 of Paper No. 9, the Examiner rejects claims 71-79 and 86 under 35 U.S.C. § 102(a) or (b) over Dustin *et al.*, *J. Immunol. 137*:245 (July 1, 1986).[4] The Examiner contends that:

> [t]he claims recited above all embrace forms of ICAM-1 that are identical to those taught by Dustin *et al. i.e.* the claims encompass ICAM-1 recombinantly-produced in cell lines which would provide the same type of glycosylation as the native cell lines taught by Dustin *et al.* This rejection may be withdrawn if a signed copy of the 1.132 declaration is made of record in this application. (Office Action at Pages 9-10).

Applicants respectfully traverse this ground for rejection.

Applicants submit that the presently pending claims are fully supported by priority parent U.S. Patent Application Serial No. 07/045,963, filed May 4, 1987. Thus, the Dustin article does not qualify as prior art under 35 U.S.C. § 102(b), since it was published less than one year before Applicants' effective filing date. To effectively remove the Dustin article as prior art under 35 U.S.C. § 102(a), Applicants herein submit a copy of the Declaration under 37 C.F.R. § 1.132 which was filed in parent U.S. Application Serial No. 07/515,478 on May 19, 1993.[5] In view of the Declaration filed May 19, 1993 in the parent application, Applicants submit that the Dustin article no longer qualifies as prior art under either 35 U.S.C. § 102(a) or 35 U.S.C. § 102(b). Applicants respectfully request that this rejection be withdrawn.

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[4] The rejection of claim 86 under 35 U.S.C. § 102(a) or (b) is apparently in error in view of the cancellation of claims 84-86 in the response filed October 15, 1997.

[5] The Declaration under 37 C.F.R. § 1.132 filed in parent U.S. Patent Application Serial No. 07/515,478 on May 19, 1993, is referred to as "Appendix A" on the post card, a copy of which is attached herein as proof of the filing date in the U.S. Patent and Trademark Office.

V. Rejection under 35 U.S.C. § 102(e)

At pages 10-12, item 6 of Paper No. 9, the Examiner rejects claims 71-79 under 35 U.S.C. § 102(e) as being anticipated by Greve, U.S. Patent No. 5,589,453 (priority to 9/1/88). The Examiner contends that:

> [t]he cited patent, columns 4-7, teaches human rhinovirus receptor protein (now referred to as ICAM-1) prepared from HeLa cells with an Mr of about 95,000 Da and tryptic fragments of ICAM-1. Claims 71-74 are anticipated because the prior art HRRP (ICAM-1) would inherently have the biological activities of native ICAM-1, such as antigenicity, ability to bind LFA-1, lymphocytes or HRV. Greve specifically teaches that ICAM-1 binds to HRV, see e.g. claims. The molecular mass limitations of claims 75-78 are anticipated by the HRRP (ICAM-1) of Greve *et al* because the 95,000 Da ICAM-1 protein of Greve has been interpreted as being "about" 72-91 kDa, 76.5-97 kDa, 114 kDa and 97 kDa thus meeting the limitations of claims 75-78. HRRP of Greve (ICAM-1) would inherently have the amino acid sequence of Figure 8, thus meeting the limitation of claim. ... The eukaryotically-expressed ICAM-1 of claims 84 and 86 embraces the 95,000 Da HRRP (ICAM-1) of Greve[6]. (Office Action at pages 10-11).

The Examiner also states "there appears no basis for priority for product claims limited to 'at least one biological activity of native ICAM-1' where that activity may be interpreted to embrace HRV-binding fragments of ICAM." (Paper No. 9 at 11-12.) Applicants respectfully traverse this ground for rejection.

Applicants invention as instantly claimed relates, *inter alia*, to purified or isolated ICAM-1 preparations substantially free of natural contaminants where the ICAM-1 is capable of binding to LFA-1, Mac-1, or p150,95. Support for the presently claimed invention can be found, *inter*

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[6] Whether or not the eukaryotically-expressed ICAM-1 of claims 84 and 86 embraces the 95,000 Da HRRP (ICAM-1) of Greve is not at issue in this Response because claims 84-86 were canceled in the Response filed October 15, 1997.

alia, at pages 11-13 of priority Application no. 07/045,963. Applicants submit that all of the currently pending claims are entitled to priority under 35 U.S.C. § 120 from the U.S. Patent Application Serial No. 07/045,963 priority application, filed May 4, 1987. Accordingly, Greve does not qualify as prior art under 35 U.S.C. § 102(e). Therefore, Applicants respectfully request that this ground for rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned directly at (202) 371-2653.

Prompt and favorable consideration of this Amendment is respectfully requested.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. In the event an extension of time is necessary to prevent the abandonment of this application not accounted for herein, such

an extension is specifically requested and the requisite fee should also be charged to our Deposit Account.

Respectfully submitted,

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